### Male Liver Top 10 Genes Ranked by Potency of Perturbation (Sorted by BMD Median)

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| --- | --- | --- | --- | --- | --- |
| **Gene Symbol** | Entrez Gene IDs | Probe IDs | BMD1Std (BMDL1std-BMDU1std) in mg/kg | Maximum Fold Change | Direction of Expression Change |
| **egr1** | 24330 | EGR1\_8533 | 0.750 (0.186-4.702) | 4.2 | DOWN |
| **zfp354a** | 24522 | ZFP354A\_10203 | 0.835 (0.271-2.999) | 4.6 | DOWN |
| **tsku** | 308843 | TSKU\_10094 | 1.384 (0.541-4.109) | 3.0 | DOWN |
| **cyp7a1** | 25428 | CYP7A1\_8430 | 5.721 (0.985-22.363) | 4.6 | DOWN |
| **gsta2** | 24422 | GSTA2\_8756 | 5.725 (1.686-19.439) | 2.3 | UP |
| **gsta5** | 494499 | GSTA2\_8756 | 5.725 (1.686-19.439) | 2.3 | UP |
| **crot** | 83842 | CROT\_8384 | 7.423 (5.757-10.316) | 6.0 | UP |
| **slc27a2** | 65192 | SLC27A2\_9860 | 7.622 (5.499-13.393) | 2.2 | UP |
| **acaa1a** | 24157 | ACAA1A\_7954 | 8.417 (7.129-10.157) | 13.3 | UP |
| **acaa1b** | 501072 | ACAA1A\_7954 | 8.417 (7.129-10.157) | 13.3 | UP |

Descriptions of orthologous human genes are shown due to the increased detail that is available in public resources such as UniprotKB (<https://www.uniprot.org/uniprot/>) and Entrez Gene (<https://www.ncbi.nlm.nih.gov/gene/>). Human UniprotKB was used as primary resource due to the greater breadth of annotation and depth of functional detail that is provided. Rat UniprotKB was used as the second resource if the primary source did not provide a detailed description of function. Human Entrez gene summary was used as third resource.  Rat Entrez gene summary was used as the fourth resource.

**Gene definition version:** https://cebs.niehs.nih.gov/cebs/study/002-00600-0002-000-0 V05282021

**Egr1:** *Human Uniprot function (Human EGR1):* Transcriptional regulator (PubMed20121949). Recognizes and binds to the DNA sequence 5'-GCG(T/G)GGGCG-3'(EGR-site) in the promoter region of target genes (By similarity). Binds double-stranded target DNA, irrespective of the cytosine methylation status (PubMed25258363, PubMed25999311). Regulates the transcription of numerous target genes, and thereby plays an important role in regulating the response to growth factors, DNA damage, and ischemia. Plays a role in the regulation of cell survival, proliferation and cell death. Activates expression of p53/TP53 and TGFB1, and thereby helps prevent tumor formation. Required for normal progress through mitosis and normal proliferation of hepatocytes after partial hepatectomy. Mediates responses to ischemia and hypoxia; regulates the expression of proteins such as IL1B and CXCL2 that are involved in inflammatory processes and development of tissue damage after ischemia. Regulates biosynthesis of luteinizing hormone (LHB) in the pituitary (By similarity). Regulates the amplitude of the expression rhythms of clock genes ARNTL/BMAL1, PER2 and NR1D1 in the liver via the activation of PER1 (clock repressor) transcription. Regulates the rhythmic expression of core-clock gene ARNTL/BMAL1 in the suprachiasmatic nucleus (SCN) (By similarity). {ECO0000250|UniProtKBP08046, ECO0000269|PubMed20121949, ECO0000269|PubMed25258363, ECO0000269|PubMed25999311}.

**Zfp354a:** *Rat Uniprot Function (Human ZNF354A):* It may play a role in renal development and may also be involved in the repair of the kidney after ischemia-reperfusion or folic acid administration.

**Tsku:** *Human Uniprot function (Human TSKU):* Contributes to various developmental events and other processes such as wound healing and cholesterol homeostasis through its interactions with multiple signaling pathways. Wnt signaling inhibitor which competes with WNT2B for binding to Wnt receptor FZD4 and represses WNT2B-dependent development of the peripheral eye. Plays a role in regulating the hair cycle by controlling TGFB1 signaling. Required for the development of the anterior commissure in the brain by inhibiting neurite outgrowth. Essential for terminal differentiation of hippocampal neural stem cells. Plays a role in regulating bone elongation and bone mass by modulating growth plate chondrocyte function and overall body size. Required for development of the inner ear through its involvement in stereocilia formation in inner hair cells. Facilitates wound healing by inhibiting secretion of TGFB1 from macrophages which prevents myofibroblast differentiation, maintaining inflammatory cell quiescence. Plays a role in cholesterol homeostasis by reducing circulating high-density lipoprotein cholesterol, lowering cholesterol efflux capacity and decreasing cholesterol-to-bile acid conversion in the liver. In one study, shown to negatively regulate sympathetic innervation in brown fat, leading to reduced energy expenditure. In another study, shown not to affect brown fat thermogenic capacity, body weight gain or glucose homeostasis.

**Cyp7a1:** *Human Uniprot function (Human CYP7A1):* A cytochrome P450 monooxygenase involved in the metabolism of endogenous cholesterol and its oxygenated derivatives (oxysterols) (PubMed11013305, PubMed12077124, PubMed19965590, PubMed2384150, PubMed21813643). Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (CPR; NADPH-ferrihemoprotein reductase) (PubMed2384150, PubMed11013305, PubMed12077124, PubMed19965590, PubMed21813643). Functions as a critical regulatory enzyme of bile acid biosynthesis and cholesterol homeostasis. Catalyzes the hydroxylation of carbon hydrogen bond at 7-alpha position of cholesterol, a rate-limiting step in cholesterol catabolism and bile acid biosynthesis (PubMed12077124, PubMed19965590, PubMed2384150). 7-alpha hydroxylates several oxysterols, including 4beta-hydroxycholesterol and 24-hydroxycholesterol (PubMed11013305, PubMed12077124). Catalyzes the oxidation of the 7,8 double bond of 7-dehydrocholesterol and lathosterol with direct and predominant formation of the 7-keto derivatives (PubMed21813643). {ECO0000269|PubMed11013305, ECO0000269|PubMed12077124, ECO0000269|PubMed19965590, ECO0000269|PubMed21813643, ECO0000269|PubMed2384150}.

**Gsta2:** *Human Uniprot function (Human GSTA2):* Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles.

**Gsta5:** *Rat Uniprot Function (Human GSTA5):* Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles.

**Crot:** *Human Uniprot function (Human CROT):* Beta-oxidation of fatty acids. The highest activity concerns the C6 to C10 chain length substrate. Converts the end product of pristanic acid beta oxidation, 4,8-dimethylnonanoyl-CoA, to its corresponding carnitine ester. {ECO0000269|PubMed10486279}.

**Slc27a2:** *Human Uniprot function (Human SLC27A2):* Acyl CoA synthetase that activates long-chain and very long-chain fatty acids (VLCFAs) by catalyzing the formation of fatty acyl-CoA (PubMed10198260, PubMed10749848, PubMed11980911). Can also activate branched-chain fatty acids such as phytanic acid and pristanic acid (PubMed10198260). Does not activate C24 bile acids, cholate and chenodeoxycholate (PubMed11980911). In vitro, activates 3-alpha,7-alpha,12-alpha-trihydroxy-5-beta-cholestanate (THCA), the C27 precursor of cholic acid deriving from the de novo synthesis from cholesterol (PubMed11980911). Exhibits long-chain fatty acids (LCFA) transport activity and plays an important role in hepatic fatty acid uptake (PubMed20530735). {ECO0000269|PubMed10198260, ECO0000269|PubMed10749848, ECO0000269|PubMed11980911, ECO0000269|PubMed20530735}.; FUNCTION [Isoform 1] Exhibits both long-chain fatty acids (LCFA) transport activity and acyl CoA synthetase towards very long-chain fatty acids (PubMed21768100). Shows a preference for generating CoA derivatives of n-3 fatty acids, which are preferentially trafficked into phosphatidylinositol (PubMed21768100). {ECO0000269|PubMed21768100}.; FUNCTION [Isoform 2] Exhibits long-chain fatty acids (LCFA) transport activity but lacks acyl CoA synthetase towards very long-chain fatty acids. {ECO0000269|PubMed21768100}.

**Acaa1a:** *Human Entrez Gene Summary (Human ACAA1):* This gene encodes an enzyme operative in the beta-oxidation system of the peroxisomes. Deficiency of this enzyme leads to pseudo-Zellweger syndrome. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jul 2008]

**Acaa1b:** *Human Entrez Gene Summary (Human ACAA1):* This gene encodes an enzyme operative in the beta-oxidation system of the peroxisomes. Deficiency of this enzyme leads to pseudo-Zellweger syndrome. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jul 2008]

### Female Liver Top 10 Genes Ranked by Potency of Perturbation (Sorted by BMD Median)

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| --- | --- | --- | --- | --- | --- |
| **Gene Symbol** | Entrez Gene IDs | Probe IDs | BMD1Std (BMDL1std-BMDU1std) in mg/kg | Maximum Fold Change | Direction of Expression Change |
| **a2m** | 24153 | A2M\_7932 | 1.163 (0.179-7.061) | 2.3 | DOWN |
| **loc100911545** | 100911545 | A2M\_7932 | 1.163 (0.179-7.061) | 2.3 | DOWN |
| **dao** | 114027 | DAO\_8437 | 6.134 (2.436-16.203) | 2.1 | UP |
| **ephx2** | 65030 | EPHX2\_33282 | 6.441 (2.664-17.347) | 2.4 | UP |
| **ehhadh** | 171142 | EHHADH\_8534 | 7.300 (5.266-11.878) | 4.0 | UP |
| **cyp2b1** | 24300 | CYP2B1\_32451 | 7.456 (5.106-13.104) | 31.5 | UP |
| **loc108348266** | 108348266 | CYP2B1\_32451 | 7.456 (5.106-13.104) | 31.5 | UP |
| **cyp2c6v1** | 293989 | CYP2C6V1\_33169 | 9.829 (7.252-14.982) | 2.4 | UP |
| **loc100911718** | 100911718 | CYP2C6V1\_33169 | 9.829 (7.252-14.982) | 2.4 | UP |
| **ech1** | 64526 | ECH1\_8516 | 9.874 (6.591-19.440) | 3.6 | UP |

Descriptions of orthologous human genes are shown due to the increased detail that is available in public resources such as UniprotKB (<https://www.uniprot.org/uniprot/>) and Entrez Gene (<https://www.ncbi.nlm.nih.gov/gene/>). Human UniprotKB was used as primary resource due to the greater breadth of annotation and depth of functional detail that is provided. Rat UniprotKB was used as the second resource if the primary source did not provide a detailed description of function. Human Entrez gene summary was used as third resource.  Rat Entrez gene summary was used as the fourth resource.

**Gene definition version:** https://cebs.niehs.nih.gov/cebs/study/002-00600-0002-000-0 V05282021

**A2m:** *Human Uniprot function (Human A2M):* Is able to inhibit all four classes of proteinases by a unique 'trapping' mechanism. This protein has a peptide stretch, called the 'bait region' which contains specific cleavage sites for different proteinases. When a proteinase cleaves the bait region, a conformational change is induced in the protein which traps the proteinase. The entrapped enzyme remains active against low molecular weight substrates (activity against high molecular weight substrates is greatly reduced). Following cleavage in the bait region, a thioester bond is hydrolyzed and mediates the covalent binding of the protein to the proteinase.

**LOC100911545:** *Human Uniprot function (Human A2M):* Is able to inhibit all four classes of proteinases by a unique 'trapping' mechanism. This protein has a peptide stretch, called the 'bait region' which contains specific cleavage sites for different proteinases. When a proteinase cleaves the bait region, a conformational change is induced in the protein which traps the proteinase. The entrapped enzyme remains active against low molecular weight substrates (activity against high molecular weight substrates is greatly reduced). Following cleavage in the bait region, a thioester bond is hydrolyzed and mediates the covalent binding of the protein to the proteinase. A2MG\_HUMAN,P01023

**Dao:** *Human Uniprot function (Human DAO):* Regulates the level of the neuromodulator D-serine in the brain. Has high activity towards D-DOPA and contributes to dopamine synthesis. Could act as a detoxifying agent which removes D-amino acids accumulated during aging. Acts on a variety of D-amino acids with a preference for those having small hydrophobic side chains followed by those bearing polar, aromatic, and basic groups. Does not act on acidic amino acids. {ECO0000269|PubMed17303072}.

**Ephx2:** *Human Uniprot function (Human EPHX2):* Bifunctional enzyme (PubMed12574510). The C-terminal domain has epoxide hydrolase activity and acts on epoxides (alkene oxides, oxiranes) and arene oxides (PubMed12869654, PubMed12574510, PubMed22798687). Plays a role in xenobiotic metabolism by degrading potentially toxic epoxides (By similarity). Also determines steady-state levels of physiological mediators (PubMed12869654, PubMed12574510, PubMed22798687, PubMed21217101). {ECO0000250|UniProtKBP80299, ECO0000269|PubMed12574508, ECO0000269|PubMed12574510, ECO0000269|PubMed12869654, ECO0000269|PubMed21217101, ECO0000269|PubMed22798687}.; FUNCTION Bifunctional enzyme (PubMed12574510). The N-terminal domain has lipid phosphatase activity, with the highest activity towards threo-9,10-phosphonooxy-hydroxy-octadecanoic acid, followed by erythro-9,10-phosphonooxy-hydroxy-octadecanoic acid, 12-phosphonooxy-octadec-9Z-enoic acid and 12-phosphonooxy-octadec-9E-enoic acid (PubMed12574510). Has phosphatase activity toward lyso-glycerophospholipids with also some lower activity toward lysolipids of sphingolipid and isoprenoid phosphates (PubMed22217705, PubMed22387545). {ECO0000269|PubMed12574510, ECO0000269|PubMed22217705, ECO0000269|PubMed22387545}.

**Ehhadh:** *Human Uniprot function (Human EHHADH):* Peroxisomal trifunctional enzyme possessing 2-enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, and delta 3, delta 2-enoyl-CoA isomerase activities. Catalyzes two of the four reactions of the long straight chain fatty acids peroxisomal beta-oxidation pathway. Optimal isomerase for 2,5 double bonds into 3,5 form isomerization in a range of enoyl-CoA species (Probable). Also able to isomerize both 3-cis and 3-trans double bonds into the 2-trans form in a range of enoyl-CoA species (By similarity). With HSD17B4, catalyzes the hydration of trans-2-enoyl-CoA and the dehydrogenation of 3-hydroxyacyl-CoA, but with opposite chiral specificity (PubMed15060085). Regulates the amount of medium-chain dicarboxylic fatty acids which are essential regulators of all fatty acid oxidation pathways (By similarity). Also involved in the degradation of long-chain dicarboxylic acids through peroxisomal beta-oxidation (PubMed15060085). {ECO0000250|UniProtKBP07896, ECO0000250|UniProtKBQ9DBM2, ECO0000269|PubMed15060085, ECO0000305|PubMed15060085}.

**Cyp2b1:** *Human Uniprot function (Human CYP2B6):* A cytochrome P450 monooxygenase involved in the metabolism of endocannabinoids and steroids (PubMed21289075, PubMed12865317). Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (NADPH--hemoprotein reductase). Catalyzes the epoxidation of double bonds of arachidonoylethanolamide (anandamide) to 8,9-, 11,12-, and 14,15-epoxyeicosatrienoic acid ethanolamides (EpETrE-EAs), potentially modulating endocannabinoid system signaling (PubMed21289075). Hydroxylates steroid hormones, including testosterone at C-16 and estrogens at C-2 (PubMed21289075, PubMed12865317). Plays a role in the oxidative metabolism of xenobiotics, including plant lipids and drugs (PubMed11695850, PubMed22909231). Acts as a 1,4-cineole 2-exo-monooxygenase (PubMed11695850). {ECO0000269|PubMed11695850, ECO0000269|PubMed12865317, ECO0000269|PubMed21289075, ECO0000269|PubMed22909231}.; FUNCTION Allele 2B6\*9 Has low affinity for anandamide and can only produce 11,12 EpETrE-EAs. {ECO0000269|PubMed21289075}.

**LOC108348266:** *Human Uniprot function (Human CYP2B6):* A cytochrome P450 monooxygenase involved in the metabolism of endocannabinoids and steroids (PubMed21289075, PubMed12865317). Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (NADPH--hemoprotein reductase). Catalyzes the epoxidation of double bonds of arachidonoylethanolamide (anandamide) to 8,9-, 11,12-, and 14,15-epoxyeicosatrienoic acid ethanolamides (EpETrE-EAs), potentially modulating endocannabinoid system signaling (PubMed21289075). Hydroxylates steroid hormones, including testosterone at C-16 and estrogens at C-2 (PubMed21289075, PubMed12865317). Plays a role in the oxidative metabolism of xenobiotics, including plant lipids and drugs (PubMed11695850, PubMed22909231). Acts as a 1,4-cineole 2-exo-monooxygenase (PubMed11695850). CP2B6\_HUMAN,P20813

**Cyp2c6v1:** *Human Uniprot function (Human CYP2C19):* A cytochrome P450 monooxygenase involved in the metabolism of polyunsaturated fatty acids (PUFA) (PubMed18577768, PubMed19965576, PubMed20972997). Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (NADPH--hemoprotein reductase) (PubMed18577768, PubMed19965576, PubMed20972997). Catalyzes the hydroxylation of carbon-hydrogen bonds. Hydroxylates PUFA specifically at the omega-1 position (PubMed18577768). Catalyzes the epoxidation of double bonds of PUFA (PubMed20972997, PubMed19965576). Also metabolizes plant monoterpenes such as limonene. Oxygenates (R)- and (S)-limonene to produce carveol and perillyl alcohol (PubMed11950794). Responsible for the metabolism of a number of therapeutic agents such as the anticonvulsant drug S-mephenytoin, omeprazole, proguanil, certain barbiturates, diazepam, propranolol, citalopram and imipramine. Hydroxylates fenbendazole at the 4' position (PubMed23959307). {ECO0000269|PubMed11950794, ECO0000269|PubMed18577768, ECO0000269|PubMed19965576, ECO0000269|PubMed20972997, ECO0000269|PubMed23959307}.

**LOC100911718:** *Human Uniprot function (Human CYP2C18):* A cytochrome P450 monooxygenase involved in retinoid metabolism. Hydroxylates all trans-retinoic acid (atRA) to 4-hydroxyretinoate and may modulate atRA signaling and clearance. Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (CPR; NADPH-ferrihemoprotein reductase). CP2CI\_HUMAN,P33260

**Ech1:** *Human Uniprot function (Human ECH1):* Isomerization of 3-trans,5-cis-dienoyl-CoA to 2-trans,4-trans-dienoyl-CoA. {ECO0000250|UniProtKBQ62651}.